REMARKS

Claims 6, 8-10, 12-15, 29-32 and 34-37 are pending and under examination in the subject application. No claim has been added, canceled or amended herein. Accordingly, claims 6, 8-10, 12-15, 29-32 and 34-37 are still pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's objections and rejections made in the April 23, 2002 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides methods of treating or preventing thrombosis, and decreasing plasma fibrinogen. These methods comprise administering a tumor necrosis factor antagonist to a subject diagnosed as suffering from or at risk of thrombosis.

This invention is based on applicants' *surprising discovery* that inhibiting the biological activity of TNFα reduces fibrinogen levels in subjects suffering from or at risk of thrombosis. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating and preventing thrombosis in subjects diagnosed as suffering from or at risk thereof.

Rejection Under 35 U.S.C. §102(a)

The Examiner rejected claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 under 35 U.S.C. §102(a) as allegedly anticipated by Hommes, et al. (Gastroenterology, 1995, Vol. 108, No. 4, suppl., p. A838) as "evidenced" by Leardi, et al. (Italian Journal of Surgical Sciences, 1983, Vol. 13, pp. 197-201) and Le, et al. (U.S. Patent No. 5,919,452).

In response to the Examiner's rejection, applicants respectfully traverse. Applicants incorporate herein by reference their remarks made in the January 2, 2002 Amendment, and make the following additional remarks to underscore their position.

Briefly, claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 provide methods of treating or preventing thrombosis and decreasing plasma fibrinogen in a subject diagnosed as suffering from or at risk of thrombosis. These methods comprise administering to the subject a therapeutically effective amount of a TNF antagonist.

To anticipate the claimed method, Hommes, et al. would have to teach each and every element thereof, specifically, treatment and prophylaxis in a subject *diagnosed as suffering from or at risk of thrombosis*. They fail to do this.

As stated previously, Hommes, et al. teach that the treatment of *Crohn's disease* patients with chimeric monoclonal antibody cA2 decreases "thrombin generation" and "endothelial activation-markers". Hommes, et al. do not teach the treatment or prevention of thrombosis, nor do they teach a decrease of plasma fibrinogen

levels. In fact, nowhere do Hommes, et al. even mention the terms "thrombosis" and "plasma fibrinogen". The Examiner makes an impermissible leap in the assumption that decreasing thrombin generation and endothelial activation-markers necessarily decreases the condition of "thrombosis" itself.

Leardi, et al. disclose that there is a higher incidence of *thromboembolism* in patients with Crohn's disease. According to the Merriam-Webster Medical Dictionary (http://www.intelihealth.com), thromboembolism is the blocking of a blood vessel by a particle that has *broken away* from a blood clot at its site of formation. Thromboembolism is a different condition than thrombosis, which is defined as the formation or presence of a blood clot within a blood vessel (thrombus). Thrombus is defined as a blood clot within a blood vessel which *remains attached to its place of origin*. Applicants annex hereto as Exhibits A, B and C these definitions of thromboembolism, thrombosis and thrombus, respectively. Therefore, Leardi, et al. do *not* serve as evidence that Hommes, et al. teach each and every element of the claimed method. Furthermore, Leardi, et al. do not teach the use of TNF antagonists to decrease thrombosis or hyperfibrinogenemia. In fact nowhere do Leardi, et al. even mention the treatment of Crohn's disease, or more specifically, thrombosis and elevated plasma fibrinogen levels, with *any* TNF antagonists.

Le, et al. also do *not* serve as evidence that Hommes, et al. teach each and every element of the claimed method, nor do they cure the deficiencies of Hommes, et al. and Leardi, et al. Le, et al. disclose the treatment of certain TNFα-mediated diseases with chimeric monoclonal antibody cA2 and antibodies which compete

therewith. Le, et al. do not teach the use of these antibodies to treat or prevent thrombosis, or to decrease plasma fibrinogen levels. Like Hommes, et al. and Leardi, et al., Le, et al. also fail to teach treatment or prophylaxis in subjects diagnosed as suffering from or at risk of thrombosis.

For these reasons, Hommes, et al., as "evidenced" by Leardi, et al. and Le, et al., fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 satisfy the requirements of 35 U.S.C. §102(a).

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 6 and 8 under 35 U.S.C. §102(b) as allegedly anticipated by Arii, et al. (Circulation, 1994, Vol. 90, No. 4, part 2, p. I522, abstract No. 2811), Vertrees, et al. (ASAIO Journal, 1994, Vol. 40, pp. M554-M559), or Wakefield, et al. (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that each of the above cited references fails to teach each and every element of the rejected claims.

The rejected claims are discussed above.

Arii, et al. provide data suggesting that TNF may induce myocardial slippage after myocardial infarction. However, Arii, et al. do not teach a method of treating or preventing *any* disorder in a subject, and in particular, do not teach the treatment or prevention of thrombosis. Indeed, nowhere do Arii, et al. mention the term thrombosis.

The Examiner asserts, however, that "the claimed method is inherent in every disclosure of the administration of the claimed antibody to a subject, as prevention necessarily embodies the administration of the claimed antibody before the onset of thrombosis." This is an incorrect assertion. The claims of the instant invention are actually drawn to a method of "preventing thrombosis in a subject *diagnosed as having or at risk of thrombosis*". Arii, et al. do not teach, nor can the Examiner properly assume, that (1) an otherwise normal Wistar rat with a mechanically-induced myocardial infarction is a subject diagnosed as at risk of thrombosis, or (2) reduction of TNF-induced myocardial slippage after mechanically-induced myocardial infarction in otherwise normal Wistar rats by treatment with anti-TNF antibody necessarily prevents thrombosis.

Vertrees, et al. teach that anti-TNFα monoclonal antibody pre-treatment in the swine model of cardiopulmonary bypass (CPB) reduces CPB-associated leukocyte changes and may help ameliorate clinical manifestations of post-pump inflammatory response syndrome. Vertrees, et al. disclose that one of the possible post-operative effects of post-pump inflammatory response syndrome is "coagulopathy", or disease affecting blood coagulation. Vertrees, et al. do not teach a method of treating or preventing *thrombosis* in a subject diagnosed as suffering from or at risk of thrombosis.

Moreover, Vertrees, et al. do not specify thrombosis as a coagulopathy, nor do they even mention the term thrombosis.

Wakefield, et al. teach that anti-TNF antibodies partially reduce vein wall neutrophil extravasation, and thus partially inhibit the vein wall inflammatory response which occurs as a *result* of venous thrombosis. Wakefield, et al. suggest that a decrease in the vein wall inflammatory response may result in a decline in the manifestations of chronic venous insufficiency, a syndrome which occurs *after* venous thrombosis. However, Wakefield, et al. do not teach the treatment or prevention of thrombosis itself.

Therefore, Arii, et al., Vertrees, et al. and Wakefield, et al. all fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 6 and 8 satisfy the requirements of 35 U.S.C. §102(b).

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 6, 8, 9, 29, 30 and 31 under 35 U.S.C. §103(a) as allegedly unpatentable over Hommes, et al. as "evidenced" by Leardi, et al. and Le, et al. in view of Dhainaut, et al. (Critical Care Medicine, 1995, Vol. 13, pp. 197-201).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Again, claims 6, 8 and 9 provide a method of treating or preventing thrombosis. Claims 29, 30 and 31 provide a method of decreasing plasma fibrinogen. The methods of claims 6, 8, 9, 29, 30 and 31 comprise administering a TNF antagonist to a subject diagnosed as suffering from or at risk of thrombosis. The TNF antagonist can be an anti-TNF antibody or antigen-binding fragment thereof.

The methods of this invention are based on the surprising discovery that inhibiting the biological activity of TNFα reduces fibrinogen levels in subjects suffering from or at risk of thrombosis. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating and preventing thrombosis in subjects diagnosed as suffering from or at risk thereof.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must be a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, the teachings of Hommes, et al., as evidenced by Leardi, et al. and Le, et al. in view of Dhainaut, et al., would have to teach or suggest every element of the claims, which they do not do.

Again, Hommes, et al. do not teach the treatment or prevention of thrombosis, or a decrease of plasma fibrinogen levels, nor do they mention the terms "thrombosis" and "plasma fibrinogen".

Combining Hommes, et al. with Dhainaut, et al. does not cure this deficiency. Dhainaut, et al. teach the use of an anti-TNF antibody in the treatment of *septic shock*. Dhainaut, et al. do not teach treatment or prevention of thrombosis, or the decrease of elevated fibrinogen levels.

Moreover, these references, when combined, would also have to motivate one of ordinary skill to combine their teachings at the time of the invention. Absent a teaching of all elements of the claimed invention, one of ordinary skill would also have no motive to combine or reasonable expectation of success.

Applicants' invention is based on the surprising discovery that inhibiting TNFα activity reduces fibrinogen levels in subjects diagonsed as suffering from or at risk of suffering from thrombosis. At the time of this application, this finding was unknown to those skilled in the art. Applicants reassert that by ignoring this fact, the Examiner makes an impermissible leap by asserting that the "successful" use of TNF antagonists against Crohn's disease and sepsis/septic shock is predictive of success against the wholly distinct disease of thrombosis.

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references teach or suggest every element of the claims, or create a motive to combine or expectation of success. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 9, 29, 30 and 31 over Hommes, et al. as "evidenced" by Leardi, et al. and Le, et al. in view of Dhainaut, et al.

The Examiner also rejected claims 6 and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Fisher, et al. (Critical Care Medicine, 1993, Vol. 21, pp. 318-327) in view of Hooper, et al. (Blood, 1994, Vol. 84, pp. 483-489) or Jolin, et al. (Acta Anaesthesiologica Scandinavica, Supplementum, 1991, Vol. 95, pp. 40-52).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The rejected claims are discussed above.

Fisher, et al., in view of Hooper, et al. or Jolin, et al., fail to teach or suggest every element of the claims.

Fisher, et al. teach essentially what Dhainaut, et al. teach, i.e., the use of an anti-TNF antibody in the treatment of *sepsis*. Fisher, et al. do not teach treatment or prevention of thrombosis, the decrease of elevated fibrinogen levels, or the treatment of a subject diagnosed as having or at risk of thrombosis.

Again, as stated above, the mere use of TNF antagonists for the treatment or prevention of diseases generally, and sepsis/septic shock specifically, does not suggest or motivate one to use TNF antagonists in the treatment or prevention of thrombosis or elevated fibrinogen levels.

Hooper, et al. do not cure this defect. Hooper et al. teach that treatment with anti-TNFα antibodies can, via an as yet unknown mechanism, reverse the inhibitory effect of TNF on protein S levels. Hooper, et al. offer no data or other evidence that anti-TNFα antibody treatment reduces or prevents thrombosis. Indeed, Hooper, et al. acknowledge that the correlation between protein S deficiency and thrombosis is "not well documented."

Jolin, et al. also do not cure the deficiencies of Fisher, et al. because they do not teach the treatment or prevention of thrombosis. Jolin, et al. do teach methods aimed at reducing hypoxic pulmonary vasoconstriction (HPV) in the treatment of adult respiratory distress syndrome (ARDS). ARDS is a syndrome with which a myriad of diseases may be associated. As such, a large number of different ARDS mediators and vasoconstrictive agents were examined for their potential for inhibiting HPV. The Examiner has not demonstrated that *any* of these are classified as TNF antagonists. Jolin, et al. also disclose that, at the time of their study, there existed *no* exact information about the effects of HPV on coagulation factors. In fact, they do not even mention thrombosis.

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references teach or suggest every element of the claims, or create a motive to combine or expectation of success. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6 and 8 over Fisher, et al. in view of Hooper, et al. or Jolin, et al.

The Examiner also rejected claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Le, et al. (U.S. Patent No. 5,656,272) in view of Hooper, et al. or Jolin, et al.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The references and rejected claims are discussed above.

Le, et al. in view of Hooper, et al. or Jolin, et al. fail to teach or suggest every element of the claims. Le, et al. teach the treatment of Crohn's disease with chimeric monoclonal antibody cA2 and antibodies which compete therewith. Le, et al. do *not* teach the use of these antibodies to treat or prevent thrombosis, or to decrease plasma fibrinogen levels. Neither Hooper, et al. nor Jolin, et al. cure this defect for the reasons discussed above. Likewise, these references also fail to create a motive to combine or a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 over Le, et al. in view of Hooper, et al. or Jolin, et al.

In view of the above remarks, applicants maintain that claims 6, 8-10, 12-15, 29-32 and 34-37 satisfy the requirements of 35 U.S.C. §103(a).

Summary

In view of the remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $400.00 fee for a two-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
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9/23/02

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